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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,131	12/05/2001	Geoffrey Goldspink	10103-004	8321

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EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/005,131	GOLDSPINK, GEOFFREY	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-35,40-42,51,58-62,67-69,78 and 97-99* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-35,40-42,51,58-62,67-69,78 and 97-99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 2, 2007 has been entered.

Claims 1-30, 36-39, 43-50, 52-57, 63-66, 70-77, 79-96 are cancelled. Claims 31, 41, 42, 58, 68, 69 are amended. Claim 99 is new.

Claims 31-35, 40-42, 51, 58-62, 67-69, 78, 97-99 are under consideration. Per restriction requirement, February 18, 2004, the scope of analysis for the instant invention is limited to a method of treatment of an animal comprising administering a plasmid vector comprising a myosin light chain enhancer and a viral promoter operatively linked to a sequence that generates a polynucleotide sequence encoding a polypeptide of therapeutic use.

Claim Objections

Claims 31-35, 40-42, 51, 58-62, 67-69, 78, 97-99 are newly objected to because of the following informalities: claims 31, 58 comprise non-elected subject matter that was restricted, February 18, 2004. In particular, claims 31 (a)(ii) and 58 (a)(ii) include "myosin heavy chain promoter" as one of the promoters to be used in the claimed

method. Also, claim 31 (c) and 58 (c) are drawn to the use of a viral strain, which is non-elected subject matter. In the case of claims 32 and 59, the claims contain non-elected subject matter, "viral vector." Claims 32-35, 40-42, 51, 69, 97-99 depend on claim 31 and are included in the objection. Claims 59-62, 67, 68, 78, 97-99 depend on claim 58 and are included in the objection. Appropriate correction is required.

Information Disclosure Statement

Applicant has filed an Information Disclosure Statement (IDS) on July 31, 2002. The IDS has been considered.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. It is noted that references have been cited on pages 16-17, 24-25 of the specification. Should Applicant wish to have these references considered, they should be listed on an IDS and copies of the references must be provided.

Withdrawn Rejections

35 U.S.C. § 112, 2nd parag.

Applicant's arguments, see page 8 of Applicant's response, filed February 2, 2007, with respect to the rejection of claims 31, 58 have been fully considered and are persuasive. Applicant indicates that claims 31, 58 are complete. This has been found persuasive. The rejection of claims 31, 58 has been withdrawn.

35 U.S.C. § 103(a)

Applicant's arguments, see page 8-9 of Applicant's response, filed February 2, 2007, with respect to the rejection of claims 31-35, 40-42, 51 as being obvious over Goldspink et al., in view of Jeang et al. have been fully considered. Upon further consideration, the Examiner withdraws the rejection as there is no motivation to express Factor VIII (a blood clotting factor) in patients who have an alpha-galactosidase A deficiency. The rejection of claims 31-35, 40-42, 51 has been withdrawn.

New/Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 58-62, 67-69, 78, 97, 98 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In looking at the claim amendment filed December 29, 2005, claim 58 has been amended to narrow the scope of any disease to a metabolic disorder or condition related to an alpha-galactosidase A deficiency, wherein the transgene used to treat the patient is not a blood coagulation factor (claim 58, (a)(iii)). A search of the specification does not indicate any support for the invention being drawn to treatment of an alpha-galactosidase A deficiency, particular wherein the treatment does not comprise a blood coagulation factor. Claims 59-62, 67-69, 78, 97, 98 depend on claim 58 and are included in the rejection.

Claims 31-35, 40-42, 51, 58-62, 67-69, 78, 97, 98 remain rejected in modified form and new claim 99 is newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record, June 30, 2005 and April 4, 2006.

Upon further consideration, the Examiner provides the following new issues of rejection. Response to Applicant's rebuttals, filed February 2, 2007, will be provided following the new issues of rejection.

The claims are drawn to treatment of the symptoms associated with alpha-galactosidase A deficiency. According to the art, symptoms that are related to an alpha-

galactosidase activity include corneal and lenticular opacities, acroparaesthesia, angiokeratomas, hypohidrosis, proteinuria, renal failure, cardiac and cerebrovascular disease, and strokes (e.g. see Lidove et al., 2007, Int. J. Clin. Pract. 61: 293-302; page 293, under Introduction). While the claims encompass the treatment of each of these symptoms, neither the art nor the specification provide any guidance as to what genes (beyond alpha-glucosidase) would be administered to the patient such that the particular symptom of acroparaesthesia, proteinuria, or renal failure would be alleviated or treated. The claims are drawn to the use of an expression construct that comprises a myosin light chain enhancer and a viral promoter, which indicates that the construct is only expressible in the muscle. It is inferred from the construct only being expressible in muscle that the only proteins that could be expressed from muscle and having an effect in distant organs/tissues such as nerves or kidney would be secretable proteins. However, it is unclear what these secretable proteins are, such that they provide a therapeutic effect. As such, without guidance as to these proteins, an artisan cannot use the claimed invention.

In addition to this issue, following secretion of the proteins from muscle, it is unclear whether enough of the protein arrives at the target site in amounts sufficient to effect any therapy. This was discussed previously in the Office Action of June 30, 2005, pages 11-12. According to the art, circulating proteins are rapidly proteolyzed by enzymes found in the bloodstream and/or are taken up by the liver (e.g. see Allen, Jr. et al., U.S. Patent 5,433,946, patented July 18, 1995). Further, according to the art and specification, the development of a humoral response (i.e. the production of neutralizing

antibodies) reduces therapeutic efficacy of gene therapy of replacement enzyme treatment (Chu, U.S. Patent Application Publication, US 2006/0663733 A1, see also specification, page 14, lines 24-25). As such, it is unclear whether any amount of protein secreted using the claimed method is effective in treating any condition associated with an alpha-galactosidase A deficiency.

The claims encompass the use of a genomic sequence that is homologous to a eukaryotic sequence or a viral sequence (e.g. claims 41, 42, 68, 69). According to the specification, vectors comprising sequences homologous to eukaryotic genomic sequences or viral sequences are envisioned to be used as this will allow the introduction of the expression cassette into the genome of eukaryotic cells or viruses by homologous recombination (specification, pages 6-7, under "B. Vectors"). With regard to using sequence that is homologous to a eukaryotic genomic sequence, it is inferred from the specification that one possible way of carrying out the claimed method is to replace the defective gene of interest with wild type sequence. However, because the art teaches that many proteins belong to families and share similar sequences, it is unclear how using a broad set of genomic sequences from heterologous species of animals can specifically target the defective gene of interest. For example, a BLAST search using chimpanzee HOXA7 sequence (NCBI number DQ977296, nucleic acids 729-1301, copy provided for Applicant) against human genomic sequence indicates that in addition to having homology matches in chromosome 7, the chimpanzee sequence also has homology matches on chromosome 17 (see NCBI printout). Because of this

lack of guidance regarding specifically targeting a gene of interest, an artisan is not enabled to arrive at using "homologous" sequences.

Thus, the claims are rejected.

Applicant's arguments filed February 2, 2007 have been fully considered but they are not persuasive.

Applicant indicates that at the time of filing, enzyme replacement therapy for Fabry disease was known to those skilled in the art. Applicant refers to the teachings of Schiffmann et al., 2000, PNAS, USA, 97: 365-370, wherein Schiffmann et al. demonstrate that a single i/v infusion of alpha-galactosidase A prepared from transfected human fibroblasts was well tolerated and significantly reduced GB3 levels in the liver (Applicant's response, page 5, 2nd parag. under Rejection under 35 U.S.C. § 112, 1st paragraph.). In response, this is not persuasive. First, the teaching of Schiffmann et al. is post-filing and thus does not indicate that enzyme replacement therapy for Fabry disease was well known in the art. It is noted that the instant Application has priority to foreign Application 9708526.0, filed April 25, 1997, in the United Kingdom. Second, the teaching of Schiffmann et al. is about protein administration; the instant invention is drawn to gene therapy. The issues of gene therapy are different from those of protein therapy and thus the teachings of Schiffmann et al. are not germane to the instant discussion. Applicant also indicates the teachings of Eng et al., 2001, N. Engl. J. Med., 345: 9-16 (Applicant's response, page 6, 2nd parag.). Again, this is not persuasive because Eng et al. teaches protein administration and not nucleic acid administration. Also, Eng et al. is post-filing art.

With regard the US Patent 6,066,626, Applicant indicates that the patent teaches non-viral and viral transgenes encoding a biologically active human lysosomal gene that was able to infect and transfect and sustain expression of the enzyme transgene in mouse cells (Applicant's response, page 6, 4th parag.). In response, the patent is post-filing art and thus does not enable the instant invention.

Applicant refers to the teachings of Jung and colleagues (Jung et al., 2001, PNAS, USA, 98: 2676-2681) (Applicant's response, page 6, 5th parag.). In response, this is not persuasive because Jung et al. is post-filing art and thus, does not indicate that the invention was enabled at the time of invention.

Applicant refers to the teachings of Qin et al., 2001, PNAS, USA, 98: 3428-3433 to indicate gene therapy of Fabry disease. In response, this is post-filing art and does not indicate that the invention was enabled at the time of filing.

Applicant indicates that the National Institutes of Health (NIH), Clinical Center reported a gene therapy study for Gaucher's and Fabry disease. The study was conducted from January 1988 and completed in April 2002 and revealed that a retroviral construct, containing glucocerebrosidase cDNA driven by the MoLV promoter, was effective in transferring copies of genes responsible for making lacking enzymes into the cells of patients with Gaucher's or Fabry disease (Applicant's response, page 8, 3rd parag.). In response, the Examiner cannot make a clear determination of whether the teachings provided by NIH would have enabled the claimed invention at the time of filing without looking at the NIH's publication. Applicant has not provided a copy of the study and in a search on the internet for the study, the Examiner has not found any

publications. In addition to this, it is not entirely clear whether Applicant's response was intended to indicate that expression of glucocerebrosidase would treat Fabry disease. If such is the case, nothing in the art indicates that glucocerebrosidase would treat Fabry disease. According to the art, glucocerebrosidase is associated with Gaucher's disease; nothing in the art indicates that there is any etiology/pathology associated with glucocerebrosidase and Fabry disease (e.g. see Mehta, 2003, BMJ, 327: 462-436, page 462, 1st col., 2nd parag and 4th parag.).

Thus, the claims remain rejected.

Claims 31-35, 40-42, 51, 58-62, 67-69, 78, 97-99 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The final Written Description Examination guidelines that were published on January 5, 2001 (66 FR 1099; available at http://www.uspto.gov/web/menu/current.html#register).

The written description requirement for a claimed genus is satisfied by sufficient description of a representative number of species by actual reduction to practice and by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties by functional characteristics coupled with a known or disclosed

correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicant were in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The claims, as written, broadly encompass a wide variety of metabolic disorders of conditions related to an alpha-galactosidase A deficiency that could be treated. According to the art, symptoms that are related to an alpha-galactosidase activity include corneal and lenticular opacities, acroparaesthesia, angiokeratomas, hypohidrosis, proteinuria, renal failure, cardiac and cerebrovascular disease, and strokes (e.g. see Lidove et al., 2007, Int. J. Clin. Pract. 61: 293-302; page 293, under Introduction). While it is implied from the specification that it is envisioned that administering transgene construct comprising a nucleic acid sequence encoding alpha-galactosidase protein would ameliorate one or some of the symptoms associated with an alpha-galactosidase A deficiency, the claims are not so limited. The claims encompass treatment of these conditions, using a wide variety of heterologous gene(s) (e.g. claims 51, 78); however, the specification provides no guidance as to what structure/function of a protein is envisioned to be used to treat the wide variety of

symptoms, such as corneal and lenticular opacities or renal failure. Along the same line, the specification does not provide any guidance of a genus of proteins which are envisioned to be used to treat acroparaesthesia or stroke.

In addition to this issue, a BLAST search of the human alpha-galactosidase gene (GenBank number: NM_000169.2) indicates that only the human and mouse sequences were known at the time of filing (see BLAST printout). (While the spider monkey sequence, BLAST printout page 4, was entered into GenBank in 1998, this is a partial sequence and does not provide any guidance on the % identity of the sequence with the entire human sequence.) While the art provides guidance for the human and mouse sequence, neither the art nor the specification provide guidance for other alpha-galactosidase sequences such the genus of alpha-galactosidase sequences can be claimed.

In addition to this issue, the claims are drawn to the use of genomic sequence that is homologous to a eukaryotic genomic sequence or a viral genomic sequence (e.g. see claims 41, 42, 68, 69). While it is generally understood that homologous means a certain amount of sequence identity between two sequences, the specification does not teach what structures are envisioned between genomic sequences of genes, such that appropriate homologous sequences across species of eukaryotes can be selected. For example, the specification does not provide guidance to discriminate between nucleic acids that encode a family of proteins, such that the appropriate family member is selected. See also Enablement rejection, above.

The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicant's effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision all the possible variant nucleic acid sequences which would hybridize but do not encode an alpha-galactosidase protein and all the possible variant nucleic acid sequences that encode proteins that treat a symptom associated with an alpha-galactosidase deficiency. Nor can an artisan identify genomic DNA that is homologous to another species of animal or virus. Thus, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only human and mouse alpha-galactosidase meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Joanne Hama
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